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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/509,648	CHARETTE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,16-19 and 22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,16-19 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Prosecution Application

The Request for Continued Examination (RCE) filed on 27 April 2004 under 37 CFR 1.114 based on parent Application No. 09/509,648 is acceptable and an RCE has been established. An action on the RCE follows.

Status of Application, Amendments and/or Claims

The amendment of 26 May 2004 has been entered in full. Claims 1-4, 10, 12, and 22-23 are amended. Claims 13-15, 20-21, and 27-32 are cancelled.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-12, 16-19, and 22-26 are under consideration in the instant application. The claims also read upon the following species: Alzheimer's disease from the disorder group, cytokine antagonist from the agent capable of releasing morphogen activity group, 2-p-bromocinnamylaminoethyl)-isoquinolinesulfonamide from the protein kinase A inhibitor group, SEQ ID NO: 2 from the morphogen amino acid sequence group, OP-1 from the morphogen group, and retinoid receptor from the molecule that binds an endogenous ligand group.

Withdrawn Objections and/or Rejections

1. The rejections to claims 2-3, 8-12, 16-19, and 22-26 under 35 U.S.C. 112, second paragraph, as set forth at pg 14-15 of the previous Office Action (27 August 2003) are *withdrawn in part* in view of the amended claims (27 April 2004). Please see section on 35 U.S.C. 112, second paragraph below.

Specification

2. The disclosure is objected to because of the following informalities:

2a. Patent applications are referenced throughout the disclosure (pg 1, lines 14-15; pg 21, lines 8-9; pg 25, line 25; pg 35, line 11). The status of the applications must be updated. The basis for this objection is set forth at pg 3-4 of the previous Office Action (27 August 2003) and at pg 4 of the Office Action of 13 November 2002.

Applicant's arguments (27 April 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant argues that if the Examiner can provide basis for the request, Applicant will consider amending the specification accordingly.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, MPEP 608.01(p) recites:

> Prior to allowance of an application that incorporates essential material by reference to a pending U.S. application, the examiner shall determine if the referenced application has been published or issued as a patent. If the referenced application has been published or issued as a patent, the examiner shall enter the U.S. Patent Application Publication No. or the U.S. Patent No. of the referenced application in the specification of the referencing application (see MPEP § 1302.04). If the referenced application has not been published or issued as a patent, applicant will be required to amend the disclosure of the referencing application to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating the amendatory material consists of the same material incorporated by reference in the referencing application.

Claim Objections

3. The objections to claims 8-9, 11, 16-17, 19, and 26 regarding the issue that the claims are not limited to the elected species are maintained and held in abeyance until allowable subject matter is identified.

35 USC § 112, first paragraph

4. Claims 1-12, 16-19, and 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing leukemia inhibitory factor (LIF)-induced dendritic retraction comprising adding an antibody against gp130 to sympathetic neurons *in vitro* that have been treated with LIF and osteogenic protein-1 (OP-1) and wherein said antibody reduces LIF-induced dendritic retraction, *does not* reasonably provide enablement for a method for potentiating morphogen activity, a method for promoting neuronal cell growth, a method for treating a disorder characterized by neuronal cell loss, or a method for treating a neurodegenerative disorder comprising administering to a mammal a composition comprising a molecule that overcomes morphogen inhibition. Additionally, the specification is enabling for a method of reducing ciliary neurotrophic factor (CNTF)-induced dendritic retraction comprising adding phosphatidylinositol-specific phospholipase C (PI-PLC) to sympathetic neurons *in vitro* before the neurons have been treated with CNTF and osteogenic protein-1 (OP-1) and wherein said PI-PLC reduces CNTF-induced dendritic retraction. The specification is also enabling for a method of reducing the inhibitory effects of LIF on OP-1 stimulated dendritic growth comprising adding an anti-LIF antibody to sympathetic neurons *in vitro* that have been treated with LIF and OP-1 and wherein said antibody reduces the inhibition of LIF on OP-1 stimulated dendritic growth. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-12, 16-19, and 22-26 are directed to a method for potentiating morphogen activity comprising administering to a mammal a composition, the composition comprising a

molecule that overcomes morphogen inhibition, thereby potentiating morphogen activity. The claims recite a method for promoting neuronal cell growth and a method for treating a disorder characterized by neuronal cell loss comprising administering to a mammal a composition, the composition comprising a molecule that overcomes morphogen inhibition, so as to potentiate growth-promoting effects of endogenous morphogens thereby promoting neuronal cell growth. The claims recite a method for treating a neurodegenerative disorder comprising administering to a mammal a composition, the composition comprising a molecule that overcomes morphogen inhibition, so as to potentiate morphogen activity, stimulating neuronal growth by morphogens to treat a neurodegenerative disorder. The claims recite that the morphogen activity is endogenous or the result of an exogenously provided morphogen. The claims also recite that the molecule that overcomes morphogen inhibition is a cytokine antagonist, more specifically a neuropoietic cytokine antagonist. The claims recite that the neuropoietic antagonist is a LIF antagonist or a CNTF antagonist. The claims also recite that the morphogen comprises an amino acid sequence having at least 70% homology with the C-terminal seven-cysteine skeleton of human OP-1, residues 330-431 of SEQ ID NO: 2. The claims recite that the molecule binds an endogenous ligand for a retinoid receptor. The claims are directed to a molecule that is a cAMP-dependent messenger pathway inhibitor, specifically a protein kinase A inhibitor ((2-p-bromocinnamylaminoethyl)-isoquinolinesulfonamide).

Applicant's arguments (27 April 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the specification adequately enables the complete scope of the invention. Applicant states that when claiming a genus, Applicant need only provide a sufficient

description of a representative number of species. Applicant submits that examples show various compounds that relieve the inhibition of OP-1, thereby potentiating the OP-1 induced growth of neuronal cells, provide sufficient guidance to enable the practice of the claimed invention. Applicant contends that the specification describes an antibody to gp130, which can be used to reduce LIF-induced dendritic retraction. Applicant argues that the specification describes PI-PLC pretreatment reduced CNTF-induced dendritic retraction. Applicant states that the specification discloses how cAMP can inhibit dendritic growth. Applicant indicates that PKA inhibitor H89 and sterically constrained enantiomers of cAMP and dibutyl cAMP were identified as drugs that interfere with cAMP signaling. Applicant argues that based on this data, one skilled in the art would have thought and been able to use these inhibitors to counter dendritic growth inhibition by cAMP.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that the instant specification teaches that an antibody against gp130 reduces LIF-induced dendritic retraction *in vitro*, PI-PLC reduces CNTF-induced dendritic retraction *in vitro*, and an anti-LIF antibody reduces the inhibition of LIF on OP-1 stimulated dendritic growth *in vitro*. However, these are only three examples of a broad class of molecules, as recited in the claims. The Examiner has broadly interpreted the term "molecule" in the claims to encompass nucleic acids, peptides, antibodies, inorganic compounds, organic compounds, etc. For example, everything on earth is comprised of molecules. The specification of the instant application does not teach any methods or working examples that administer all possible molecules or compositions comprising a molecule and a morphogen to a mammal that overcome morphogen inhibition to potentiate morphogen activity, promote neuronal growth, treat a

disorder characterized by neuronal cell loss, or treat a neurodegenerative disorder. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis".

The instant fact pattern closely resembles that in Ex parte Maizel, 27 USPQ2d 1662 (BPAI 1992). In Ex parte Maizel, the claimed invention was directed to compounds which were defined in terms of function rather than sequence (i.e., "biologically functional equivalents"). The only disclosed compound in Ex parte Maizel was the full length, naturally occurring protein. The Board found that there was no reasonable correlation between the scope of exclusive right desired by Appellant and the scope of enablement set forth in the patent application. Even though Appellant in Ex parte Maizel urged that the biologically functional equivalents would consist of proteins having amino acid substitutions wherein the substituted amino acids have similar hydrophobicity and charge characteristics such that the substitutions are "conservative" and do not modify the basic functional equivalents of the protein, the Board found that the specification did not support such a definition, and that the claims encompassed an unduly broad number of compounds. Such is the instant situation because the claims simply recite molecules that overcome morphogen inhibition. Clearly, anti-gp130 antibodies, anti-LIF antibodies, PI-PLC, and H89 do not support claims to all possible molecules, given the lack of guidance regarding what specific molecules overcome morphogen inhibition and potentiate morphogen activity, promote neuronal cell growth, and treat a disorder.

Furthermore, the claims of instant application broadly recite a method for potentiating morphogen activity, promoting neuronal cell growth, treating a disorder characterized by neuronal cell loss, and treating a neurodegenerative disorder comprising administering a molecule that overcomes *morphogen* inhibition. However, undue experimentation would be required of the skilled artisan to determine which morphogen is being inhibited and then administer a molecule to overcome the inhibition and potentiate the morphogen's activity. For example, the instant specification discloses that "the terms "morphogen", "bone morphogeny", "bone morphogenic protein", "BMP", "morphogenic protein" and "morphogenetic protein" all embrace the class of proteins typified by human osteogenic protein 1 (hOP-1)...Other known and useful morphogens include, but are not limited to, BMP-2, BMP-3, BMP-3b, BMP-4, BMP-5, BMP-6, BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-15, GDF-1, GDF-2, GDF-3, GDF-4, GDF-6, GDF-7, GDF-8, GDF-9, GDF-10, GDF-11, GDF-12, 60A, NODAL, UNIVIN, SCREW, ADMP, and NEURAL, and morphogenically-active amino acid variants of any thereof" (pg 4, lines 4-14). Extensive combinations of different target morphogens and molecules would have to be tested to achieve the desired results as recited in the claims. Such experimentation is considered undue. The specification of the instant application also does not direct one skilled in the art how to proceed with testing all possible combinations.

(ii) Applicant also asserts that it has been shown that at least 4 molecules (PD98059, U0126, and two dominant negative forms of MEK1 and ERK2) overcome morphogen inhibition and enhance growth stimulation by OP-1. Applicant refers to the manuscript of Exhibit B (which has published as Kim et al., J. Neurosci 24(13): 3304-3312, 2004). Applicant submits that all four

molecules possess one or more of the characteristics described in the specification (pg 31) and are evaluated by a method as described in Examples 3.1 of the specification. Applicant argues that PD98059, U0126, and dominant negative forms of MEK1 and ERK2 represent diverse molecules, structurally completely different from each other and from the antibody against gp130 (see specification). Applicant asserts multiple, diverse molecules have been shown to relieve OP-1 inhibition, thereby enabling the practice of the claimed invention.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, PD98059, U0126, and dominant negative forms of MEK1 and ERK2 inhibit MEK1 or ERK2, respectively. The exposure of these agents alone (as required by the most of the claims) to sympathetic neurons does not induce dendritic growth (see for example, Figure 2A, Figures 4-6). These agents only *enhance the effects* of BMP-7 (a morphogen) on dendritic growth (Figures 2-6). Therefore, the molecules in Kim et al. do not overcome morphogen inhibition, as required by the claims, since the experiments disclosed in the references do not teach that any morphogens are inhibited. Additionally, Kim et al. does not teach that the PD98059, U0126, and dominant negative forms of MEK1 and ERK2 relieve OP-1 inhibition, as indicated by Applicant. It is noted that the instant claims do not specifically recite that OP-1 inhibition is relieved.

(iii) Applicant asserts that the specification outlines a procedure for administering to a mammal a molecule capable of releasing inhibition on morphogen activity. Applicant submits that the specification describes various routes of administration and formulation for such administration. Applicant indicates that an example carrier is given as well as the general

description of an acceptable carrier or vehicle. Applicant contends that an example of interval of administration is given and at pg 10, line 23 of WO 94/03600, a soluble complex form of morphogenic proteins is described, including how to make, test, and use them.

Applicant's arguments have been fully considered but are not found to be persuasive. Such broad brush assertions of making, screening, and administering compounds do not constitute adequate guidance to practice the claimed method, but rather constitute an invitation to experiment empirally to determine how to practice the suggested method to obtain the therapeutic results required by the claims. The specification discloses numerous modes of administration as well as a broad range of dosage amounts (pg 22). Although Applicant submits that parameters such as dosages and timing and methods of administration of therapeutic agents may need to be optimized and that optimization is routine, there is little guidance in the specification for one skilled in the art to determine these optimal conditions. Such trial and error experimentation is considered undue. The skilled artisan must still resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration of all possible molecules that overcome morphogen inhibition. The claims of the instant application encompass any method of administration and any dosage for any length of time. Furthermore, it is noted that compositions of morphogenic proteins and methods of making and using them are disclosed WO 94/03600, rather than molecules that overcome inhibition, as required by the claims.

(iv) Applicant argues that *in vivo* data show that Applicant's observations *in vitro* are in good correlation with *in vivo* data, indicating the *in vitro* conditions used in Applicant's experiments reflect *in vivo* conditions. Applicant briefly reviews Snider et al. (J Neurosci 8(7): 2828-2834, 1998), Lein et al. (Neuron 15 : 597-605, 1995), Granholm et al. (Cell Transplantation 8(1) : 75-85, 1999), Gou et al. (J Neurosci 19 :2113-2121, 1999), and Morikawa et al. (Neurosci 100(4) : 841-848, 2000). Applicant also argues that Chung et al. (Circulation 107: 3133-3140, 2003) and Clari et al. (Circulation 105(21) : E183, 2002) (cited by the Examiner in the previous Office Action) are inapposite to the instant application because they disease treatments for heart failure and not morphogens/neuronal cell growth. Applicant also submits that in vitro models for heart failure are different from the in vitro model for neuronal cell growth.

Applicant's arguments have been fully considered but are not found to be persuasive. The references cited by Applicant, which support *in vitro* experiments, indicate that NGF stimulates dendritic growth *in vivo*, OP-1 stimulates nerve cell growth *in vivo*, and that LIF inhibits dendritic growth *in vivo*. However, the specification of the instant application and the references do not teach the administration of a molecule or a composition comprising a molecule and morphogen to a mammal that overcomes morphogen inhibition to potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, or treat a neurodegenerative disorder. The instant claims do not recite the administration of a morphogen to a mammal (as in the cited references), but rather, a composition comprising a molecule or a molecule-morphogen that overcomes morphogen inhibition. The claims of the instant application also do not recite contact of a molecule with any specific neurons. As discussed in the previous Office Action (27 August 2003), the state of the art is such that for the

nervous system, hypotheses that hold well *in vitro* rarely, if ever, translate directly into the clinic (Lo, DC, Current Drug Discovery, June 2002, pg 27-30). Applicant asserts the Lo's discussion is primarily about the correlation of genetic markers and/or expression levels of proteins with a disease. However, the Examiner has interpreted the Lo reference as a review article which discusses the approaches and challenges for efficient drug discovery of the CNS, including animal models, live-tissue, cell-type specificity, throughput and genetic manipulation (pg 27-29). For example, Lo also states that "the majority of both research and pharmaceutical development experience over the last few decades indicates that when given neural cell types are removed from their tissue context, the balance of the genetic and biochemical pathways is altered so considerably that their roles in neuronal function are no longer predictive of either normal or diseased states. Thus, using the exact cell types that are specifically affected in disease within their natural tissue context is critical in maintaining relevance to the physiological state of the cells and tissue that will be faced in the clinical setting" (pg 28, 1st full paragraph in 3rd col).

Furthermore, the Examiner cited Chung et al. and Clari et al. in the previous Office Action (27 August 2003) to indicate the state of the art at the time the instant application was filed. Although Chung et al. and Clari et al. indicate that favorable results with therapeutic agents in experimental models of *heart failure* have not been replicated in controlled clinical trials, these references are but one example indicating that *in vitro* results are not predictive of *in vivo* results. Regarding the instant invention, one skilled in the art would not predict that the *in vitro* results with morphogens or any other molecule are predictive of *in vivo* results. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as

mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, or treat a neurodegenerative disorder by administration of a molecule that overcomes morphogen inhibition to a mammal.

(v) Applicant also disagrees with the Examiner's interpretation of Halliday et al., Steece-Collier et al., and Feigin et al. Applicant reviews the content of these three papers.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, a broad, reasonable interpretation of the claims encompasses treatment of such neurodegenerative disorders as Alzheimer's disease, Parkinson's disease, and Huntington's disease, among others, which have proven to be recalcitrant to treatment in the art (see for example, Halliday et al., Clin Exp Pharmacol Physiol 27: 1-8, 2000; Steece-Collier et al., Proc Natl Acad Sci USA 99(22): 13972-13974, 2002; Feigin et al. Curr Opin Neurol 15: 483-489, 2002). Each of these references indicates that these diseases are neurodegenerative and result in a loss of neurons. Although Applicant argues that the claimed invention relates to enhancing neuronal cell growth to compensate for neuronal death and degeneration, the claims recite promoting neuronal cell growth, treating disorders characterized by neuronal cell loss, and treating a neurodegenerative disorder, all of which broadly encompass administration of a

composition to a mammal with neurodegenerative diseases or conditions. The Examiner cited Halliday et al., Steece-Collier et al., and Feigin et al. simply to indicate the state of the art at the time the application was filed. However, undue experimentation would be required of the skilled artisan to promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, and treat a neurodegenerative disorder by administration of all possible molecules that overcome morphogen inhibition.

Additionally, there are a variety of neuronal cells encompassed by the claimed methods (see claims 2-4, for example), such as motor neurons, sensory neurons, glial cells, dopaminergic neurons, serotonergic neurons, oligodendrocytes, sympathetic neurons, Schwann cells, astrocytes, etc. since the claims only recite "neuronal cell growth" and "neuronal cell loss". A large quantity of experimentation would be required by the skilled artisan to promote the cell growth of all possible neuronal cells by the administration of any molecule or a composition comprising any molecule-morphogen.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to identify and screen all possible molecules and morphogens; to potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, and treat a neurodegenerative disorder with all possible molecules; and to determine the optimal dosage, duration, and mode of administration of all possible molecules and compositions comprising a molecule-morphogen, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of administering a molecule to a mammal, undue experimentation would be required

of the skilled artisan to make and/or use the claimed invention in its full scope.

5. Claims 1-12, 16-19, 22-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-12, 16-19, and 22-26 are directed to a method for potentiating morphogen activity comprising administering to a mammal a composition, the composition comprising a molecule that overcomes morphogen inhibition, thereby potentiating morphogen activity. The claims recite a method for promoting neuronal cell growth and a method for treating a disorder characterized by neuronal cell loss comprising administering to a mammal a composition, the composition comprising a molecule that overcomes morphogen inhibition, so as to potentiate growth-promoting effects of endogenous morphogens thereby promoting neuronal cell growth. The claims recite a method for treating a neurodegenerative disorder comprising administering to a mammal a composition, the composition comprising a molecule that overcomes morphogen inhibition, so as to potentiate morphogen activity, stimulating neuronal growth by morphogens to treat a neurodegenerative disorder. The claims recite that the morphogen activity is endogenous or the result of an exogenously provided morphogen. The claims also recite that the molecule that overcomes morphogen inhibition is a cytokine antagonist, more specifically a neuropoietic cytokine antagonist. The claims recite that the neuropoietic antagonist is a LIF antagonist or a CNTF antagonist. The claims also recite that the morphogen comprises an amino acid sequence

having at least 70% homology with the C-terminal seven-cysteine skeleton of human OP-1, residues 330-431 of SEQ ID NO: 2. The claims recite that the molecule binds an endogenous ligand for a retinoid receptor. The claims are directed to a molecule that is a cAMP-dependent messenger pathway inhibitor, specifically a protein kinase A inhibitor ((2-p-bromocinnamylaminoethyl)-isoquinolinesulfonamide).

The specification of the instant application teaches "agents that release morphogen inhibition are appreciated by persons skilled in the art to be those that interfere with or suppress known morphogen-inhibitory signalling pathways and/or morphogen-inhibitory compounds. Morphogen-inhibition releasing agents can be any of numerous compounds such as polyclonal or monoclonal antibodies, analogs, enantiomers or other inhibitors known to inhibit or interfere with the activity of morphogen-inhibitory signaling pathways and/or morphogen-inhibitory compounds" (pg 21, lines 19-24). However, the specification does not teach all possible specific molecules that overcome morphogen inhibition. The brief description in the specification of a few examples of molecules that could overcome morphogen inhibition (e.g., antibody to gp130) is not adequate written description of an entire genus of molecules.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the molecules of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The molecule itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

Therefore, only a specific molecule (such as an anti-gp130 antibody), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, second paragraph

6. Claims 1-12, 16-19, and 22-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. The term "morphogen activity" in claims 1-12, 16-19, and 22-26 is a relative term which renders the claims indefinite. The term "morphogen activity" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It cannot

be determined if "morphogen activity" means for example, inducing the migration, proliferation and differentiation of progenitor cells, inducing bone morphogenesis, or repairing non-chondrogenic tissues. The basis for this rejection is set forth at pg 15-16 of the previous Office Action (27 August 2003) and at pg 8-9 of the Office Action of 13 November 2002.

Applicant's arguments (27 April 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant argues that U.S. Applicant No. 08/445,467 (U.S. Patent 6,077,823), which is incorporated by reference into the instant specification, clearly defines morphogen activity. Thus, the claims are not indefinite.

Applicant's arguments have been fully considered but are not found to be persuasive. As indicated in the previous Office Action (27 August 2003), any and all activities may be encompassed by the term "morphogen activity". As pointed out by Applicant, the '823 patent even discloses that morphogens stimulate the proliferation of progenitor cells, stimulate the differentiation of progenitor cells, stimulate the proliferation of differentiated cell, support the growth and maintenance of differentiated cells. Applicant states that morphogens can also inhibit epithelial cell proliferation. Therefore, it is not clear from the specification or the claims what activities are or are not encompassed by this term. Additionally, it is inappropriate to read limitations in the specification into the claims. The claims must independently define the invention for which patent protection is sought.

8. The term "morphogen inhibition" in claims 1-12, 16-19, and 22-26 is a relative term which renders the claims indefinite. The term "morphogen inhibition" is not defined by the

claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It cannot be determined if "morphogen inhibition" means for example, inhibiting the migration, proliferation and differentiation of progenitor cells, inhibiting bone morphogenesis, or inhibiting the repair of non-chondrogenic tissues. The basis for this rejection is set forth at pg 16-17 of the previous Office Action (27 August 2003) and at pg 8-9 of the Office Action of 13 November 2002.

Applicant's arguments (27 April 2004), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that in view of the fact that "morphogen activity" is shown to be clearly defined, it follows that "morphogen inhibition" is the inhibition of such activity.

Applicant's arguments have been fully considered but are not found to be persuasive because it is inappropriate to read limitations in the specification into the claims. The claims must independently define the invention for which patent protection is sought. Therefore, the claims are still rejected as being indefinite because the claims do not recite a clear definition of the term "morphogen inhibition".

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Fann et al. Proc Natl Acad Sci USA 91 : 43-47, 1994 (neuropoietic cytokines)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
19 July 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER